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K.M.M. Berghuis [a,b,c,*], S. Fagioli [b,d], N.M. Maurits [e], I. Zijdewind [f], J.B.C. Marsman [g], T. Hortobágyi [a], G. Koch [c], M. Bozzali [b,h]

[a] University of Groningen, University Medical Center Groningen, Center for Human Movement Sciences, Groningen, the Netherlands
[b] IRCCS Santa Lucia Foundation, Neuroimaging Laboratory, Rome, Italy
[c] IRCCS Santa Lucia Foundation, Non-Invasive Brain Stimulation Unit, Rome, Italy
[d] University of Roma Tre, Department of Education, Rome, Italy
[e] University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, the Netherlands
[f] University of Groningen, University Medical Center Groningen, Department of Neuroscience, Groningen, the Netherlands
[g] University of Groningen, University Medical Center Groningen, Cognitive Neuroscience Center, Biomedical Sciences of Cells and Systems, Groningen, the Netherlands
[h] University of Sussex, Brighton & Sussex Medical School, Department of Neuroscience, Brighton, United Kingdom

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ABSTRACT

It is poorly understood how healthy aging affects neural mechanisms underlying motor learning. We used blood-oxygen-level dependent (BOLD) contrasts to examine age-related changes in brain activation after acquisition and consolidation (24 h) of a visuomotor tracking skill. Additionally, structural magnetic resonance imaging and diffusion tensor imaging were used to examine age-related structural changes in the brain. Older adults had reduced gray matter volume (628 ± 57 ml) and mean white matter anisotropy (0.18 ± 0.03) compared with young adults (741 ± 59 ml and 0.22 ± 0.02, respectively). Although motor performance was 53% lower in older (n = 15, mean age 63.1 years) compared with young adults (n = 15, mean age 25.5 years), motor practice improved motor performance similarly in both age groups. While executing the task, older adults showed in general greater brain activation compared with young adults. BOLD activation decreased in parietal and occipital areas after skill acquisition but activation increased in these areas after consolidation in both age groups, indicating more efficient visuospatial processing immediately after skill acquisition. Changes in deactivation in specific areas were age-dependent after consolidating the motor skill into motor memory. Young adults showed greater deactivations from post-test to retention in parietal, occipital and temporal cortices, whereas older adults showed smaller deactivation in the frontal cortex. Since learning rate was similar between age groups, age-related changes in activation patterns may be interpreted as a compensatory mechanism for age-related structural decline.

1. Introduction

Despite age-related neuroanatomical and neurophysiological changes, such as decline in gray and white matter volume (Coupe et al., 2017), reduction in white matter integrity (Salat et al., 2005), and a loss of gamma-amino-butyric-acid interneurons (Lehmann et al., 2012), healthy older adults are still able to acquire and retain new motor skills. The magnitude of motor learning can even equal that of young adults when practicing a visuomotor tracking skill (Berghuis et al., 2016; Cirillo et al., 2011). Because detrimental age-related changes involve brain areas that are activated during motor learning (Dayan and Cohen, 2011; Seidler et al., 2010), it is reasonable to expect that older compared with

Abbreviations: AFNI, analysis of functional neuroimages; ANOVA, analysis of variance; ART, artifact detection tool; BOLD, blood-oxygen-level dependent; BMI, body mass index; CRUNCH, compensation-related utilization of neural circuits hypothesis; DMN, default mode network; DTI, diffusion tensor imaging; FA, fractional anisotropy; FSL, FMRIB Software Library; GARS, Groningen activity restriction scale ; GLM, general-linear model; MD, mean diffusivity; MMSE, mini mental state examination; MPRAGE, magnetization-prepared rapid gradient-echo; (f)MRI, (functional) magnetic resonance imaging; PSQI, Pittsburgh sleep quality index; SPM, statistical parametric mapping; SPSS, statistical package for the social sciences.

* Corresponding author. Center for Human Movement Sciences, University Medical Center Groningen, A. Deusinglaan 1, 9700 AD, Groningen, the Netherlands.
E-mail address: k.m.m.berghuis@umcg.nl (K.M.M. Berghuis).

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young adults would rely on different neural mechanisms during motor learning. This might be suggestive of adaptive or compensatory strategies.

However, it is poorly understood how healthy aging affects the neural mechanisms underlying motor learning. Functional Magnetic Resonance Imaging (fMRI) studies showed that older and younger adults activate similar brain areas during sequential motor practice, such as sensorimotor, parietal, striatal and cerebellar areas but additionally, older adults activate frontal and temporal areas bilaterally (Fogel et al., 2014; Lin et al., 2012). Because age does not seem to affect the rate of motor learning in these studies, the age-related changes in activation patterns may be interpreted as a compensatory mechanism for age-related structural declines, which include reductions in gray and white matter volume (Coupe et al., 2017). The additional bilateral brain activation seen in older adults also agrees with the hemispheric asymmetry reduction in older adults (HAROLD) model, which also has been suggested as a compensatory strategy (Cabeza, 2002; Cabeza et al., 2002). In contrast, when in the early stages of visuomotor adaptation participants learned to adapt to rotated visual feedback, older compared with younger adults acquired the skill less well and meanwhile showed reduced brain activation in sensory, frontal, temporal and occipital areas, in the cingulate gyrus, insular cortex and subcortical regions such as the caudate nucleus and thalamus (Anguera et al., 2011). These studies are in accordance with the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) from the working memory literature. CRUNCH hypothesizes that the age-related decline in neural efficiency leads to compensatory recruitment of additional neural resources at low levels of cognitive demand (Reuter-Lorenz and Cappell, 2008). Conversely, when cognitive demands increase, older adults would reach a ceiling-level of activity resulting in under-activation and under-performance compared with young adults.

Brain activation recorded during motor practice identifies the involvement of putative brain areas in motor learning. However, examining *changes* in brain activation over time provides more insights into the age-related differences in the adaptive mechanisms underlying motor learning. After implicitly acquiring a motor sequence, brain activation in temporal (including the hippocampus) and prefrontal areas has been shown to increase in older but decrease in young adults (Rieckmann et al., 2010). Furthermore, older compared with young adults showed greater increases of activation from the first to the second half of training in the dorsolateral prefrontal cortex bilaterally, and in the right superior frontal and left orbitofrontal cortex. In contrast, young adults showed greater increases of activation in the right striatum, thalamus, motor, and occipital cortex, and in the cerebellum, parietal, and insular cortex bilaterally (Rieckmann et al., 2010). Additionally, young compared with older adults showed greater decreases of activation in the right orbitofrontal area. After acquiring a motor skill, this skill needs to be consolidated into motor memory to be retained. One study reported that 4 h after explicitly learning a motor sequence, brain activation increased in frontal, temporal and parietal areas, hippocampus and cerebellum in older individuals, but it decreased in young adults when participants did not have the opportunity to take a nap (Fogel et al., 2014). When participants took a nap, results were in the opposite direction (Fogel et al., 2014). Taken together, these limited available data suggest that changes in brain activation after implicit and explicit motor sequence acquisition and consolidation are age-dependent, with increases in frontal and temporal brain areas of older adults but decreases in the same brain areas of young adults after both stages of motor learning. How brain activation changes after acquisition and consolidation of a visuomotor tracking skill differs between young and older adults is unknown.

To the best of our knowledge, no fMRI study to date has examined age-related changes in brain activation over time after both the acquisition and consolidation phase. Therefore, the current study examined the effects of age on brain activation changes after acquisition and consolidation (24 h) of a visuomotor tracking skill. We hypothesized that the changes in brain activation would be age-dependent. Based on previous motor sequence studies that included visuomotor (Rieckmann et al., 2010) and explicit learning (Fogel et al., 2014) components similar to our visuomotor tracking task, we specifically expected increases in older but decreases in young adults in frontal and temporal activation after both the skill acquisition and consolidation phase. This age-dependent change in frontal and temporal activation might indicate an age-dependent reliance on cognitive control and memory while learning a motor skill. Furthermore, to be able to compare our current results with previous studies, we examined the effects of age on the average brain activation during visuomotor task execution. We expected older compared with young adults to show greater activation when executing the visuomotor task. We tested both hypotheses with a whole-brain analysis approach. When motor learning rates are similar between young and old adults, as expected based on previous findings using a similar task (Berghuis et al., 2016), any age-related differences in brain activation or in task-related modulation of brain activity would be interpreted as an alternative, compensatory strategy in older adults.

2. Methods

2.1. Participants

Healthy young ($n = 17$, 7 males, age range: 21–31, mean ± SD: 25.5 ± 2.3 years) and older ($n = 16$, 9 males, age range: 56–72; 62.6 ± 5.3 years) right-handed (Oldfield, 1971) adults participated in this study. None of them had any contraindications to undergo MRI scanning or suffered from any pain or movement restriction in their right arm. Older adults were physically and cognitively preserved, according to the Groningen Activity Restriction scale (mean score: 18.9 ± 2.5, Kempen et al., 1996) and the Mini Mental State Examination (mean score: 29.2 ± 0.8, 28–30, Folstein et al., 1975). The study was approved by the IRCCS Santa Lucia Foundation Ethics Committee in Rome, Italy, and each participant signed an informed consent in accordance with the Declaration of Helsinki prior to enrollment.

2.2. Procedure

Fig. 1 shows the study design, which included two sessions, with approximately a 24 h period in between. Participants underwent fMRI during visuomotor tracking task performance to determine brain activation before motor practice, after motor skill acquisition and after motor memory consolidation. Day 1 started with three familiarization trials of the visuomotor task. Subsequently, participants executed a pre-test, a training session and a post-test inside the MRI scanner. Each test consisted of six blocks. Participants started each block by viewing a fixation cross for 20 s, followed by performing five trials of the experimental condition, viewing of the fixation cross for 20 s, and concluding the block by performing five trials of the control condition (see section 2.3). Both pre- and post-test consisted of the same trials that appeared in a pseudorandomized order. During both the pre- and post-test, fMRI acquisition was performed. The training session consisted of four blocks of 30 trials with 30 s of fixation cross between the blocks and took place inside the MRI scanner without fMRI acquisition. At the end of the session on Day 1, an anatomical scan was acquired as an anatomical reference (see section 2.4). As sleep is known to have an influence on motor learning, which could be different across age groups (e.g. Fogel et al., 2014), we investigated whether sleep quality was similar in the two age groups. Therefore, on Day 2 (approximately 24 h after Day 1), all participants filled in the Pittsburgh Sleep Quality Index (PSQI) questionnaire concerning sleep quality and quantity over the last month and last night. Subsequently, they entered the scanner for the final fMRI session during the retention test, which consisted again of the same trials as the pre- and post-test but in a different order. Finally, Diffusion Tensor Imaging (DTI) was conducted, so that we could determine whether our group of older adults showed expected age-related changes in white matter microstructural integrity (Sullivan and Pfefferbaum, 2007).

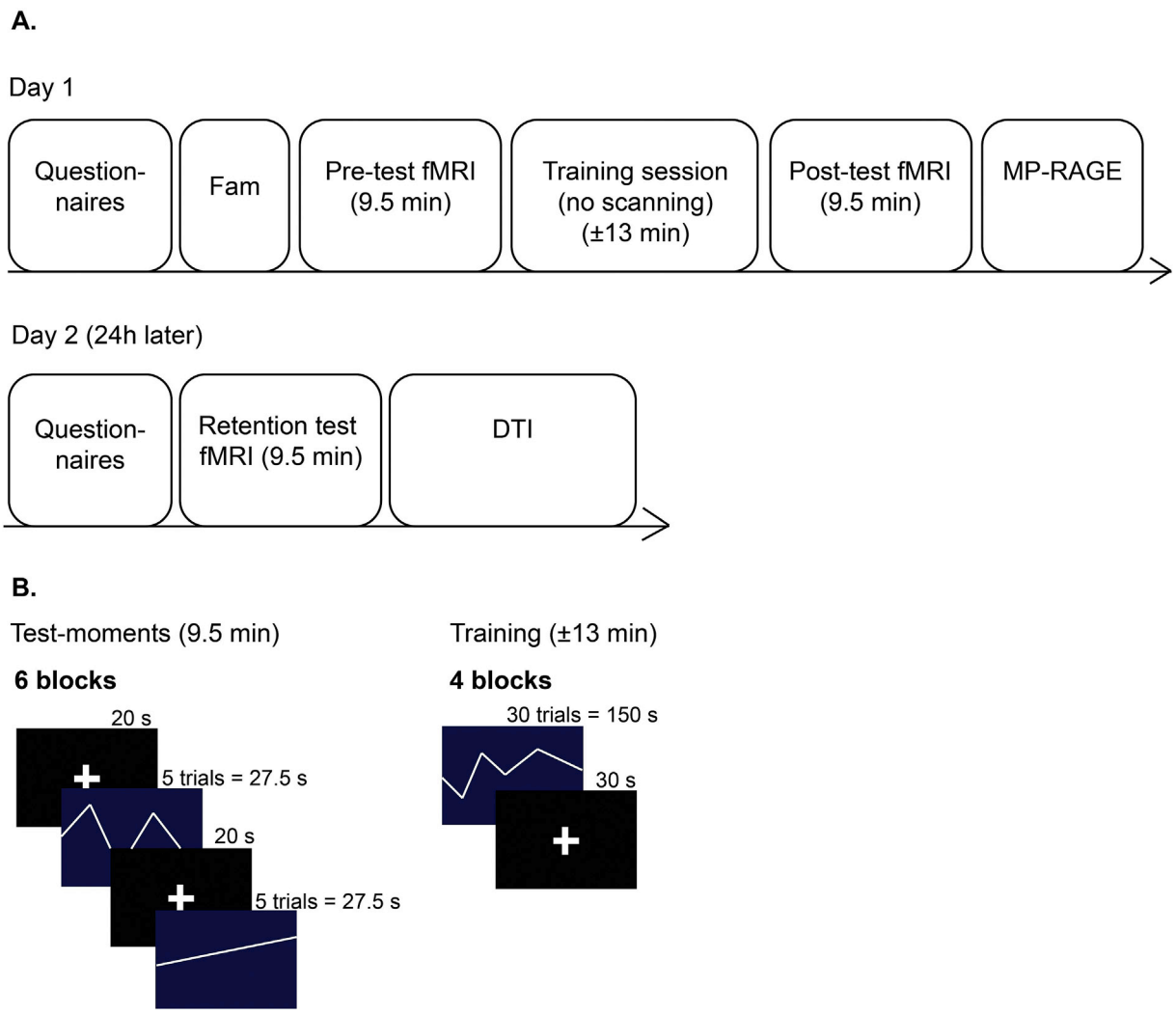

Fig. 1. The design of the study, with A) the complete study design, and B) the design for the visuomotor task in de MRI scanner with a zig-zagged experimental condition and a monotonically in- or decreasing line as a control condition. Fam, familiarization; fMRI, functional magnetic resonance imaging; MP-RAGE, Magnetization-Prepared Rapid Gradient-Echo sequence; DTI, diffusion tensor imaging.

2.3. Visuomotor task

Participants performed a visuomotor tracking task using an MR compatible manipulandum (Toxopeus et al., 2011). The manipulandum was affixed to the right side of the MR table, and the distance was adjusted to the participant's arm length. The settings were adjusted so that participants were only able to perform wrist flexion and extension in the transverse plane. Participants' right forearm was placed on cushions and participants held the grip of the manipulandum with the thumb taped to the fingers, reminding participants to perform the task with wrist- and not finger-movements. Head movements were minimized by using an adjustable padded head holder and foam pads.

The visuomotor task consisted of tracking templates using wrist flexion and extension (Berghuis et al., 2015). There were two conditions: the experimental condition consisted of zigzagged templates with four or five turns, whereas the control condition consisted of monotonically increasing or decreasing templates. The templates were presented in white on a dark blue background, and the participants' wrist position was shown in green. The experimental and control condition each had five patterns and a duration of 4, 5 or 6 s. There was a 500 ms delay between trials. The pattern and duration of the templates were pseudorandomized, such that the mean duration of a five-trial block was 5 s and that all five patterns of either the experimental or the control condition appeared once within each five-trial block. The training session consisted of five different patterns but had a similar level of difficulty as those used for the experimental condition. These trials had similar durations as the testing trials and again the patterns and durations varied pseudorandomly. The visuomotor task was projected on a screen at the head end of the MRI scanner and visible for participants through a mirror affixed to the head coil. The start of the visuomotor test-trials was synchronized with the MRI scanner by waiting for a specific slice number that was communicated from the scanner to the laptop managing the visuomotor task software.

2.4. fMRI and DTI

Brain imaging was performed with a Siemens Magnetom Allegra 3-T head-only scanning system (Siemens Medical Systems, Erlangen, Germany), equipped with a quadrature volume RF head coil. Blood-oxygen-level dependent (BOLD) contrasts were obtained using echo-planar T2*-weighted imaging with 32 slices (EPI; TR = 2.08 s, TE = 30 ms, flip angle = 70°, matrix 64 × 64, voxel size = 3 × 3 mm in-plane, slice thickness = 2.5 mm; 50% distance factor; FOV = 192 mm) providing coverage of the whole cerebral cortex. Per test, 279 functional volumes were acquired. In addition, we acquired a Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) sequence as an anatomical reference

(TR = 2.5 s, TE = 2.74 ms, voxel size 1 × 1 × 1 mm, matrix resolution 256 × 256 × 176, axial acquisition). Finally, DTI images were acquired using the following parameters: TR = 7000 ms, TE = 85 ms, 61 diffusion directions, maximum b factor = 1000 s/mm^2, isotropic resolution 2.3 mm^3. Sixty-one diffusion weighted images and seven non-diffusion weighted image (b = 0 s/mm^2) were acquired.

2.5. Data and statistical analyses

2.5.1. Analysis of participants' characteristics

Participants' characteristics were analyzed using SPSS version 24 (IBM SPSS Statistics, Armonk, NY, USA). Group differences between categorical variables (e.g. sex) were assessed with the $\chi 2$ test. Comparisons between older and young participants for continuous variables were performed using two-tailed independent t-tests. When continuous variables were not normally distributed, or in case of ordinal variables, Mann-Whitney's *U* test was performed. Significance was accepted at $\alpha = 0.05$.

2.5.2. Analysis of visuomotor task performance

The performance on the visuomotor task was analyzed in Matlab 2011a (The Mathworks Inc., Natick, MA, USA) for the experimental and control condition separately by calculating the absolute mean error of the participant's wrist joint position from the preprogrammed template. The performance value indicates an average error over the 30 trials per condition per test. A second order low-pass Butterworth filter of 5 Hz was used to filter the joint position data. Data obtained during the first second of each trial were discarded as it contained errors associated with reacting to the appearance of the template. The visuomotor performance data were not normally distributed and were therefore log-transformed. Mixed analysis of variance (ANOVA) was performed in SPSS with between-subjects factor Age (Young, Older) and within-subjects factors Time (Pre, Post, Retention) and Condition (Experimental, Control). Significance was accepted at $\alpha = 0.05$. The non-transformed data are reported in the results.

2.5.3. fMRI preprocessing and first level analysis

(f)MRI data preprocessing and first-level analysis were performed in SPM12 (Wellcome Trust Center for Neuroimaging, UCL, UK). The first four images of each EPI sequence were discarded to ensure T1 signal equilibrium. First, all functional images of each MRI session (Day1: Pre + Post and Day2: Retention) were manually reoriented. Subsequently, all functional images from all sessions were realigned to the first image of the first session and co-registered to the mean functional image. Then, images were normalized to the MNI template and a 3D Gaussian kernel of 8 mm full-width at half maximum (FWHM) was used to smooth the EPI images. Furthermore, the structural image of each participant was segmented to extract gray matter, white matter, and cerebrospinal fluid volumes. Age-related differences in these volumes were examined using an independent *t*-test in SPSS.

The exact onsets and durations of the experimental and control blocks of each participant were determined in Matlab using the experimental log-file. In the first-level analysis, brain activation during task execution (Experimental, Control) was modelled by a general linear model (GLM) for each test-moment (Pre, Post, Retention) and participant. Six motion regressors were included in the design matrix for each test-moment to control for any head movements of the participant during the scanning sessions. High-pass filtering was implemented in the design matrix using a cutoff period of 128 s to remove low-frequency drifts from the time series. Statistical parametric maps (SPMs) were computed on subject level (F and t-statistics). Contrasts that were defined in the first level analysis and used in the second level analysis were as follows: activation per condition versus baseline (e.g. ExperimentalPre), and activation at each time point with higher activation in experimental versus control condition (e.g. $Pre_{Experimental>Control}$). After the first-level analysis, Artifact Detection Tool (ART) was applied in all participants to check and correct for movement artifacts (https://www.nitrc.org/projects/artifact_detect). As the participants were explicitly told to move inside the scanner by acting on the manipulandum and considering that head motion-induced artifacts increase with age (Savalia et al., 2017), we adopted a liberal threshold to identify outliers for the global signal intensity and head motion (z-threshold = 9; movement threshold = 2 mm) while retaining an acceptable amount of data. None of the subjects had >10% outliers. No correlations between motion and timing of the experimental and control condition were detected. Subsequently, the first-level analysis was performed again, including the outliers and regressors computed by ART in the model as covariates of no interest.

2.5.4. fMRI second level analysis

Second level analyses were performed using linear mixed effects analyses (3dLME, implemented in AFNI, http://afni.nimh.nih.gov/afni/, Chen et al., 2013) because of missing data in one participant. We defined four linear mixed effects models. In the first model, we were interested in 1) the differences in brain activation between young and older adults during execution of both the experimental (Exp) and control (Contr) conditions to test the hypothesis that older adults utilize more brain activation compared with young adults in order to perform the visuomotor task and 2) the differences in brain activation between the conditions during task execution in order to examine whether there was greater brain activation when executing the experimental versus the control condition, which serves as input data for the second model. Therefore, functional images of each condition and time (ExpPre, ExpPost, ExpRetention, ContrPre, ContrPost, ContrRetention) after movement artifact correction were implemented per participant as input images in this model. Age, Condition, and Time were fixed factors. The intercept was allowed to vary across participants and was therefore a random factor. The covariance structure was an identity matrix. The following contrasts were computed using two-sided *t*-tests: Older > Young and Experimental > Control.

In the second model, we were interested in changes in brain activation over time, specific for the experimental condition. Therefore, we entered the Experimental > Control contrasted images for each participant and each time-point in an ANOVA ($Pre_{Exp>Contr}$, $Post_{Exp>Contr}$, $Retention_{Exp>Contr}$) to examine the main effect of Time (Pre, Post, Retention) and the Age × Time interaction (hence, corrected for control condition activation). Age and Time were fixed factors, and similar to model 1, the intercept was allowed to vary randomly across participants and the covariance structure was an identity matrix. The following post-hoc *t*-tests (two-sided) were specified in the model using activation masks representing the main and interaction effects to further examine the meaning of these effects: 1) changes in brain activation from one time point to another, averaged across age groups (Post > Pre, Retention > Post, and Retention > Pre); 2) differences between young and older adults in changes in brain activation over time, for example $Young_{Retention>Post} > Older_{Retention>Post}$; and 3) differences between time points within age groups, for example $Young_{Retention} > Young_{Post}$.

In addition to these first two models, two models were defined that were replicas of the first two models but now inserted whole-brain gray matter volume (%total intracranial volume) as a covariate to examine whether the expected age-related differences in gray matter had an influence on brain activation.

In all models, Monte Carlo simulation was used to correct for multiple comparisons and to determine the significant effects at cluster-level (3dClustSim, implemented in AFNI, initial threshold of p = 0.001, cluster size k > 30, 10000 iterations). Post-hoc contrasts in the second model were calculated with an uncorrected p-threshold of 0.001. Of these contrasts, only clusters greater than 10 voxels are reported in the text. Significant clusters were labelled using the Automated Anatomical Labeling atlas in MRIcron.

To understand the main and interaction effects of the fMRI analyses better, we extracted the parameter estimates of the GLM for each participant. For each cluster of the main and interaction effects, a mask

was created. For each mask, mean parameter estimates were extracted in Matlab for each condition and time point in each participant.

2.5.5. Analysis of diffusion weighted images

Diffusion weighted images were preprocessed using tools from the FMRIB Software Library (FSL, University of Oxford, UK; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and Camino (Microstructure Imaging Group, UCL, UK; http://camino.cs.ucl.ac.uk/). Diffusion weighted data were corrected for eddy current distortions and involuntary movements by affine coregistration using the FLIRT tool (part of the FMRIB Software Library). The b matrices were rotated accordingly (Leemans and Jones, 2009). The diffusion tensor was estimated in every voxel (Basser et al., 1994) and maps of fractional anisotropy (FA) and mean diffusivity (MD) were obtained. Subsequently, for each subject, average FA- and MD-values were calculated for the whole brain, which are indicators of microstructural integrity. FA measures the fraction of diffusion that is anisotropic, that is the fraction of water molecules moving in the direction of the axon, whereas MD measures the average motion of water molecules in all directions (Basser, 1995; Pierpaoli et al., 1996). To determine whether our group of older adults showed expected age-related neuronal changes, in addition to changes in gray and white matter volume as measured with structural MRI, we examined differences in whole-brain FA and MD between age groups using an independent *t*-test in SPSS.

3. Results

One older and two young adults were excluded from the data analyses because of anatomical abnormalities or artifacts. So, data from 15 young (age 25.5 ± 2.5 years) and 15 older adults (age 63.1 ± 5.2 years) were analyzed. One older participant did not understand the instructions for the motor task at the pre-test. Therefore, for this participant, we applied mean substitution for the pre-test motor performance values and only included the fMRI data of the post-test and retention test. Table 1 shows that participants' characteristics do not differ between the two age groups, except for age ($t_{20.026} = -25.28$, $p < 0.001$).

3.1. Behavioral results

Fig. 2 shows the motor performance in the experimental and control condition at the three time-points in the two age groups and Table 2 summarizes the absolute and percent changes in performance. A main effect of Time ($F_{2, 56} = 59.8$, $p < 0.001$) showed that, averaged across age groups and conditions, motor performance increased by 22% from pre-to post-test and by an additional 11% from post-test to retention test. The Age ($F_{1, 28} = 12.8$, $p = 0.001$) and Condition ($F_{11, 28} = 135.9$, $p < 0.001$) main effects showed that older compared with younger adults' motor performance was 3.2° (53%) worse and that, overall, participants performed 3.5° (37%) better at the control compared with the experimental condition. There were no Age × Time ($F_{2, 56} = 0.2$, $p = 0.790$) or Age × Condition × Time ($F_{2, 56} = 0.1$, $p = 0.929$) interactions, indicating that both age groups improved their motor performance in both conditions at similar rates.

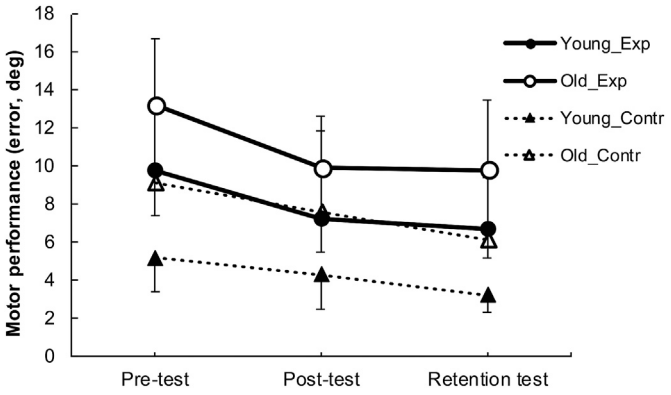

Fig. 2. Motor performance of young (filled symbols) and older adults (open symbols) on the experimental (solid line, circles) and control condition (dashed line, triangles). Motor performance is shown as mean error from the template in degrees. There were main effects of Age, Time and Condition (see section 3.1).

Table 1
Participants' characteristics.

Variable	Young adults	Older adults	Between-group difference	
	(n = 15)	(n = 15)	Test statistic	p-value
Age (y)	25.5 (2.5)	63.1 (5.2)	$t_{20.026} = -25.28$	<0.001
Sex (M/F)	6/9	9/6	$\chi^2_1 = 1.20$	0.273
Height (m)	172.3 (9.5)	167.6 (12.1)	$t_{28} = 1.18$	0.249
Mass (kg)	68.5 (16.8)	71.3 (15.0)	$t_{28} = -0.48$	0.635
BMI (kg/m^2)	22.8 (3.6)	25.2 (3.7)	$t_{28} = -1.84$	0.076
Laterality quotient	0.71 (0.17)	0.78 (0.17)	$t_{28} = -1.10$	0.282
PSQI	4.4 (2.0)	4.5 (2.4)	$t_{28} = -0.08$	0.935
Quantity of sleep (h)	6.8 (1.2)	6.8 (1.5)	Mann-Whitney U = 99.5	0.584
Quality of sleep[a]	1	1	Mann-Whitney U = 111.0	0.936
MMSE score	–	29.2 (0.8)	–	–
GARS	–	18.9 (2.5)	–	–

Values are mean (±SD). Key: BMI, body mass index; GARS, Groningen Activity Restriction Scale (18–72, the higher the score, the higher the activity restriction); MMSE, Mini Mental State Examination (>27 cognitively healthy); PSQI, Pittsburgh Sleep Quality Index (lower score is higher quality of sleep in last month); [a] Median instead of mean, 4-point Likert scale, with values between 0 and 3, denoting high and poor quality of sleep in the night before retention testing, respectively.

3.2. Structural MRI and DTI results

Older adults had a smaller gray matter volume (Older: 628 ± 57 ml; Young: 741 ± 59 ml; $t_{28} = 5.3$, $p < 0.001$) and a higher cerebrospinal fluid volume (Older: 322 ± 63 ml; Young: 230 ± 51 ml; $t_{28} = -4.4$, $p < 0.001$) compared to young adults. There were no age-related differences in white matter volume (Older: 427 ± 47 ml; Young: 444 ± 46 ml; $t_{28} = 1.0$, $p = 0.325$).

DTI results revealed that older adults had, averaged across the whole brain, a lower FA (Older: 0.18 ± 0.03; Young: 0.22 ± 0.02; $t_{28} = 3.8$, $p = 0.001$) but similar MD (Older: $1.04*10^{-9} \pm 0.19*10^{-9}$; Young: $0.99*10^{-9} \pm 0.10*10^{-9}$; $t_{22.1} = -0.9$, $p = 0.363$) when compared to young adults.

Table 2
Motor performance improvements relative to pre-test performance.

Condition	Group	Absolute improvement (°)		Percent improvement (%)	
		Pre- to post-test	Pre-test to retention	Pre- to post-test	Pre-test to retention
Experimental	Older	3.30 (2.09)	3.39 (2.18)	25.0 (12.5)	25.7 (16.4)
	Young	2.51 (1.34)	3.04 (1.76)	25.8 (11.3)	31.3 (12.9)
Control	Older	1.48 (1.62)	2.95 (1.73)	16.3 (18.6)	32.6 (15.4)
	Young	0.91 (1.38)	1.98 (1.33)	17.5 (26.2)	38.2 (14.1)

Note: positive improvements reflect an increase in motor performance. Values represent mean (SD). There were main effects of Age, Condition and Time (see section 3.1).

3.3. fMRI results

3.3.1. Comparison of BOLD-signal between age groups and conditions

The first model revealed that older compared with young adults showed greater brain activation in a wide range of brain areas (Fig. 3), including the striatum, thalamus and hippocampus, pre- and post-central gyri, frontal, temporal and occipital/parietal areas bilaterally. We examined this effect in more detail by inspecting the activation patterns during each condition at each time point. This demonstrated that in a minority of these areas this effect seems to be related to greater de-activations in young compared to older adults, including the left insular cortex, frontal areas, precuneus, calcarine cortex, and fusiform gyrus; right rolandic operculum, precentral gyrus and amygdala; and bilateral hippocampus. In the majority of the areas, however, the results were due to higher brain activations in older compared with younger adults.

Furthermore, this model showed that there was greater activation when executing the experimental compared with the control condition in bilateral motor, parietal and occipital areas and cerebellum (Fig. 4, red/yellow blobs). However, during execution of the control compared with experimental condition, activation was greater in right middle frontal gyrus and right inferior parietal/angular gyrus (Fig. 4, blue/green blobs).

When whole-brain gray matter volume was added to the first model as a covariate, all regions (with the exception of the left hippocampus) that were greater activated in the older versus young adults, were no longer significant. This indicates that age-related differences in gray matter partially explained the age-related differences in brain activation. Additionally, the right supramarginal/post-central gyrus resulted to be significantly more activated in older compared with young adults only when entering the gray matter volume as a covariate to the model.

3.3.2. Effect of time on BOLD-signal

The second model took into consideration any time-related effects specific for the experimental condition. There was a main effect of Time (Table 3) and post-hoc contrasts revealed that, across age groups, brain activation decreased from pre-to post-test in the parietal and occipital areas bilaterally, and increased back to pre-test levels from post-test to retention (Fig. 5, Supplementary materials: Table S1). Additionally, brain activation increased also from post-test to retention in the right superior/middle frontal gyrus.

3.3.3. Age by time interaction effect on BOLD-signal

The second model also revealed an Age × Time interaction, showing age-related differences in brain activation changes over time in the bilateral precuneus/posterior cingulum, left middle temporal gyrus, left inferior frontal gyrus, and left middle occipital/angular/middle temporal gyrus (Table 3, Fig. 6 left). Post-hoc contrasts showed that from post-test to retention, activation in the left inferior frontal gyrus increased in older adults but tended to decrease in young adults (Fig. 6 right, Supplementary materials: Table S2). However, in the other areas, activation decreased in young but tended to increase older adults (Fig. 6 right, Supplementary materials: Table S2). When examining these results in more detail by extracting the parameter estimates of the GLM, it appeared that during both experimental and control condition and in both age groups, there were deactivations in all clusters (see Supplementary materials: Fig S1). This indicates that there was less brain activation in these clusters during task execution compared with the rest condition at each time point. Changes in deactivation from post-test to retention occurred only when executing the experimental condition, while no changes occurred when performing the control condition. Hence, there were greater deactivations from post-test to retention in bilateral precuneus/posterior cingulum, left middle temporal gyrus and

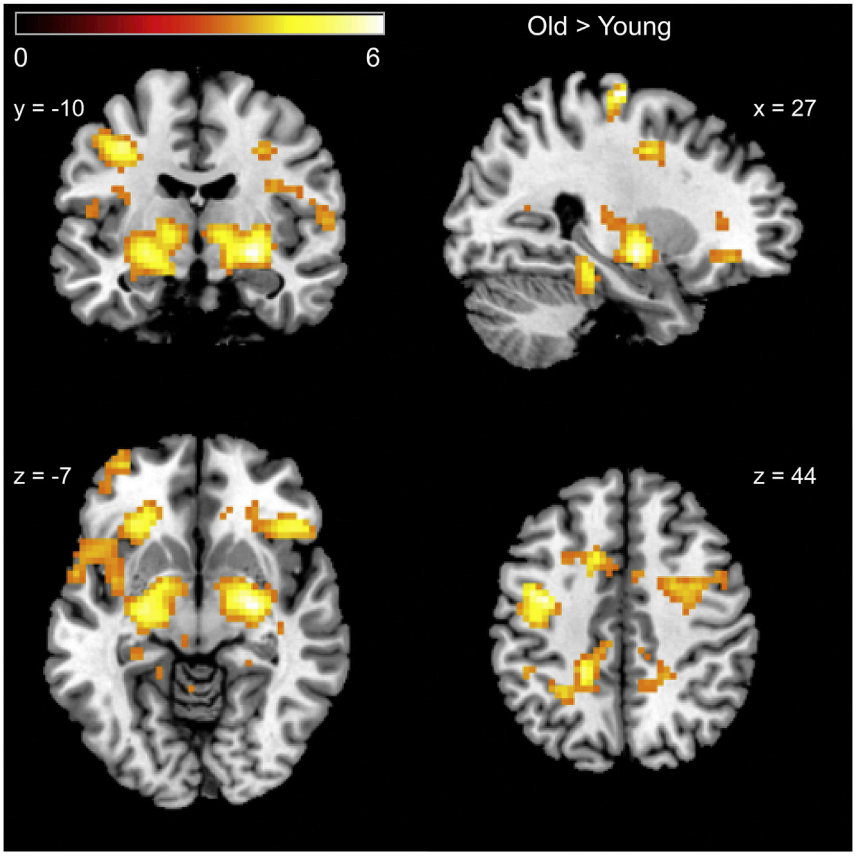

Fig. 3. Greater brain activation in older compared with young adults during the execution of the motor tasks (Z-scores). There were no regions with greater activation in young vs. older adults.

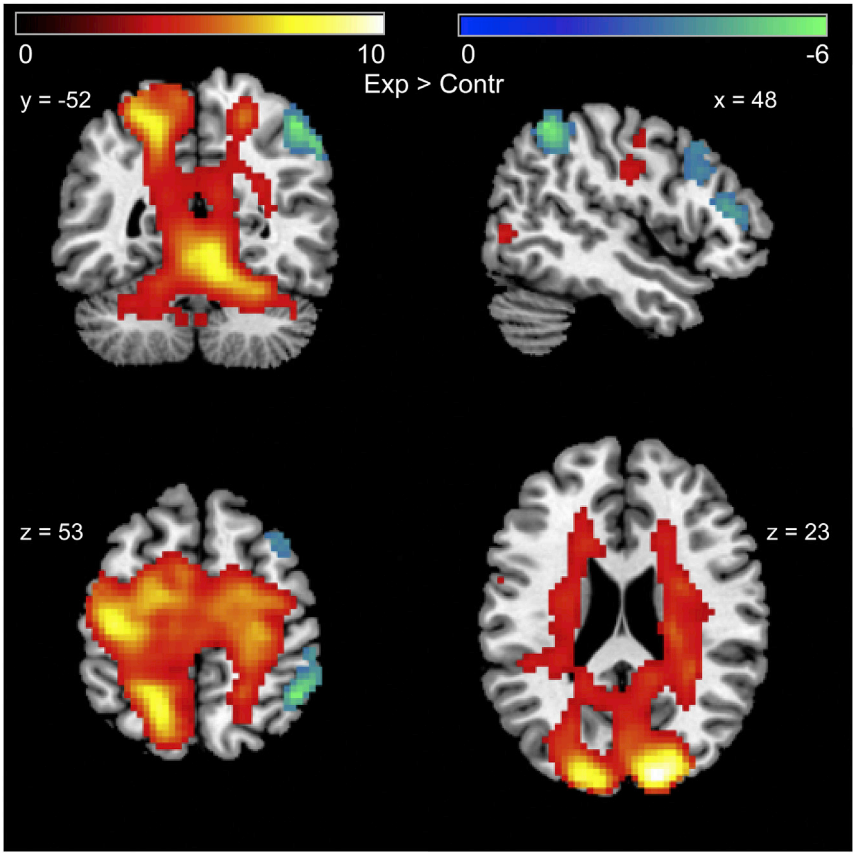

Fig. 4. Differences in brain activation between experimental and control condition, averaged across age-groups and time points (Z-scores). Red/yellow indicate greater activation in experimental condition compared with control condition, and blue/green indicate greater activation in control condition compared with experimental condition.

Table 3
Effects of Time and interaction between Age and Time on BOLD-signal.

Cluster(s)	Side	Peak voxel MNI coordinates			Cluster size (nr of voxels)	F-value
		X	Y	Z		
Time main effect						
Inferior frontal gyrus pars opercularis	L	−36	14	20	57	11.72
Superior occipital gyrus	L	−27	−73	23	68	12.16
Superior/middle occipital gyrus, precuneus, angular gyrus, middle temporal gyrus	R	21	−61	44	92	11.46
Superior/inferior parietal gyrus, precuneus, middle occipital gyrus	L	−18	−67	59	108	12.05
Middle frontal gyrus	R	33	11	59	33	11.05
Precuneus	L	−9	−58	62	31	11.97
Age × Time interaction						
Middle temporal gyrus	L	−63	−40	2	30	11.07
Inferior frontal gyrus pars triangularis	L	−54	26	14	41	12.86
Middle occipital gyrus, angular gyrus, middle temporal gyrus	L	−39	−70	32	69	11.46
Precuneus, posterior cingulum	L + R	−3	−55	17	229	14.40

Note: This model included fMRI images of Experimental > Control contrasted images for both age-groups at all time-points as input.

left middle occipital/angular/middle temporal gyrus during the experimental condition in young adults but there were no significant changes in these areas in older adults. Simultaneously, there was a trend for a smaller deactivation from post-test to retention in left inferior frontal gyrus in the older adults but no significant change was observed in the young adults. To summarize, while executing the experimental condition, from post-test to retention, there were trends for greater deactivations in young but smaller deactivations in older adults in bilateral precuneus, and left frontal, temporal, and occipital areas.

When whole-brain gray matter volume was added to the model as a covariate, the left middle temporal gyrus cluster from the Age × Time interaction of the second model was no longer significant, indicating that age-related differences in whole-brain gray matter volume partially explained the functional neural changes in this area after motor learning. There was no influence of gray matter volume on brain deactivation changes in the other clusters of the Age × Time interaction or Time main effect.

4. Discussion

We examined age-related changes in brain activation after acquisition and consolidation (24 h) of a visuomotor tracking skill. Young and older adults learned the skill to a similar extent and both age groups decreased brain activation in parietal and occipital areas bilaterally after skill acquisition. On the other hand, they increased activation in these same areas and in the right frontal cortex after motor memory consolidation. Older adults showed in general greater brain activation while executing the task. In contrast to brain activation, changes in brain deactivation were age-dependent after consolidating the motor skill into motor memory. Young adults showed greater deactivations from post-test to

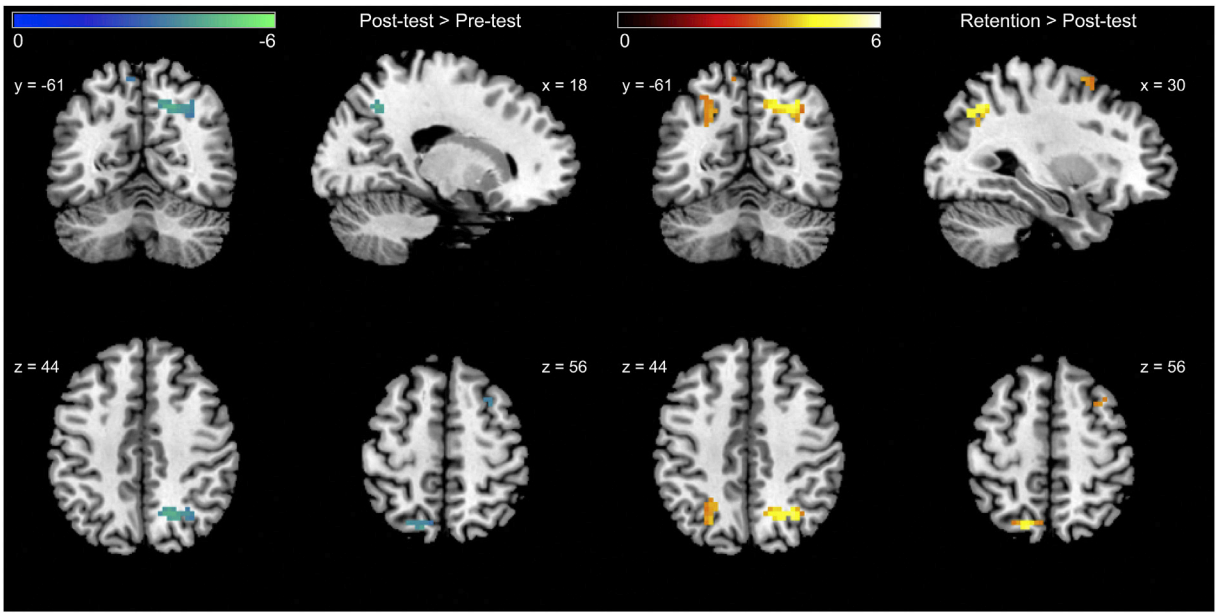

Fig. 5. Changes in brain activation from pre-to post-test (left) and post-test to retention test (right), averaged across age-groups (Z-scores). Blue/green indicate decreases and red/yellow indicate increases in brain activation over time. Experimental > Control contrasted images were used as input images in the statistical model.

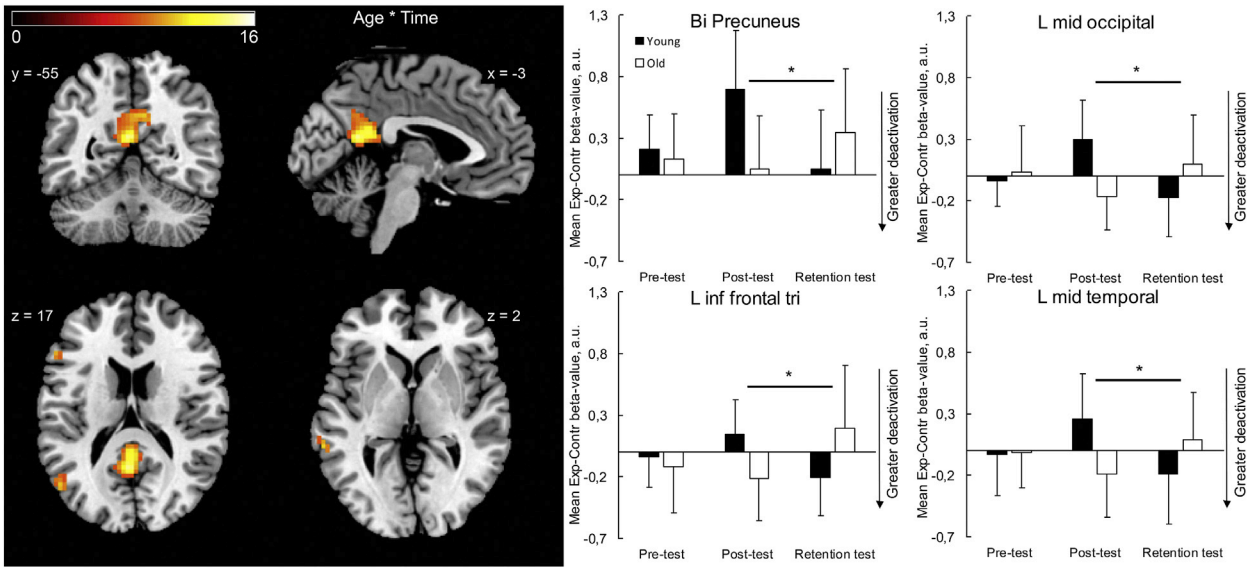

Fig. 6. Left side: Interaction of Age × Time on BOLD-signal (F-values). Experimental > Control contrasted images were used as input images in the statistical model. Right side: Mean parameter estimates in the regions of the Age × Time interaction effect (see left side) for Experimental > Control condition in both age groups. In each region, there was an interaction effect between young and older adults in changes in BOLD-signal from post-test to retention. An asterisk indicates a significant interaction between the two designated time points and the two age groups as determined by post-hoc BOLD-contrasts and corresponds to z-values < -4.

retention in the bilateral precuneus and left occipital and temporal areas, whereas older adults showed smaller deactivations in the left inferior frontal area. These results suggest that older adults use an alternative strategy compared with young adults while learning a visuomotor tracking skill, which might be a compensatory mechanism for age-related structural changes.

4.1. Learning rate is similar in older and young adults

Although older adults performed worse on the visuomotor task compared with young adults, the practice-induced improvements in performance were similar in the two age groups. This finding is consistent with previous studies, using similar tasks with the wrist (Berghuis et al., 2016), and index finger (Cirillo et al., 2011). An age-related decline in motor performance can be explained by deteriorations in nervous and neuromuscular systems with increasing age (for a review see Seidler et al., 2010). The similar learning rates in young and older adults together with the hypothesized age-related differences in brain function suggest that alternative learning strategies might occur in the older brain to compensate for age-related declines in brain structure. This will be discussed in the next sections.

4.2. Structural declines occur in the aging brain

As expected, we found age-related structural declines in the brain. Older compared with younger adults had smaller gray matter volumes,

increased cerebrospinal fluid volumes, and lower white matter anisotropy (FA). This is in agreement with previous studies (Coupe et al., 2017; Sullivan and Pfefferbaum, 2007) and indicates that our older participants are probably a representative sample of the Italian healthy aging population.

4.3. Older adults show greater brain activation when executing a visuomotor tracking task

In agreement with many studies using motor and cognitive tasks (for reviews see Reuter-Lorenz and Cappell, 2008; Ward, 2006) older compared with young adults showed greater brain activation when executing the visuomotor tracking task. This greater brain activation was shown in a wide range of brain areas, including bilateral striatum, thalamus and hippocampus, sensorimotor cortices, frontal, temporal, parietal and occipital areas. In some of these areas this effect seemed to be related to greater deactivations in young compared with older adults, including the left insular cortex, frontal areas, precuneus, calcarine cortex, and fusiform gyrus; right rolandic operculum, precentral gyrus and amygdala; and bilateral hippocampus. These results suggest that older adults rely more on striatal, thalamic, sensorimotor and temporal functions than young adults do, which could be an attempt to compensate for age-related structural declines (see section 3.2). The greater activation in older adults agrees with the CRUNCH model (Reuter-Lorenz and Cappell, 2008). However, this compensatory strategy is only partially successful since the learning rate is similar between the age groups but the performance level of older adults is 3.2° (53%) worse when compared to that of young adults. Greater striatal activation in older compared with young adults is in agreement with some (Mattay et al., 2002; Ward et al., 2008) but not with other studies (Santos Monteiro et al., 2017; Van Impe et al., 2009). The striatum is involved in feedback and decision-making (Balleine et al., 2007; Hiebert et al., 2014). We argue that the greater striatal activation we observed in older compared with young individuals might be due to their poorer performance, as demonstrated by their higher error. Finally, the result that parts of the frontal, occipital and parietal cortices are less deactivated in older adults is in agreement with the idea that with advancing age there is a dysregulation of the default mode network (DMN; Park and Reuter-Lorenz, 2009).

To summarize, it seems that by over-activating cortical and subcortical motor areas, older adults rely on compensatory strategies. Though, this interpretation warrants some caution because age-related respiratory or vascular differences could have confounded the results (D'Esposito et al., 2003; Kannurpatti et al., 2010). In other words, BOLD-signal is an indirect measure of neural activity, which is also influenced by cerebral blood flow, cerebral blood volume and cerebral blood oxygen consumption that are affected by age (D'Esposito et al., 2003; Leenders et al., 1990). Furthermore, age-related increases in muscle (co-)activation (Hortobagyi and Devita, 2006; Rozand et al., 2017) might also explain the greater brain activation in motor areas in older compared with younger adults. However, since we did not measure muscle activity, we cannot deduce this based on our data. Finally, the exact relationship between motor performance and brain activity is unclear. One possibility is that such a relationship is non-linear. Furthermore, increased brain activation could be inherent to a lower performance without necessarily indicating a compensatory strategy.

4.4. No age-related differences were demonstrated in brain activation changes

In contrast to our hypothesis (Fogel et al., 2014; Rieckmann et al., 2010), brain activation was modulated similarly over time in young and older adults. More specifically, both age groups showed a decrease of brain activation from pre-to post-test in bilateral parietal and occipital areas and increased activation in these same areas back to pre-test levels from post-test to retention. Additionally, brain activation increased also from post-test to retention in the right frontal areas. These results suggest that visual processing areas are more involved when performing the visuomotor task for the first time and after a 24 h offline period when compared to immediately after a training session. Our results agree with previous studies in young adults demonstrating that brain activation decreased when participants become more familiar with a task (Boe et al., 2012; Gobel et al., 2011). Such a reduction may reflect more efficient signal processing after motor practice. Consistent with this interpretation, a recent magnetoencephalography study showed decreased beta event-related desynchronization in occipital cortices in participants performing an isometric ankle plantarflexion target matching task (Gehringer et al., 2018). The novelty of the current study is the demonstration of more efficient visuospatial processing after a single motor training session in older adults. Our results are in line with the results by Santos Monteiro et al. (2017) who showed that after 2 weeks of motor training brain activation changed similarly over time in young and older adults. However, they demonstrated decreased activation in left temporal, bilateral frontal and right thalamic areas, whereas we found decreased activation in bilateral occipital and parietal areas.

After 24 h, brain activation increased back to pre-test levels in both age groups. This may indicate that approximately half an hour of task experience (at Day 1) may not be sufficient to retain the visuospatial processing efficiency a day later. Increased brain activation after motor memory consolidation including a night of sleep is in agreement with the limited research available in young adults, which showed increased activation in bilateral basal ganglia, bilateral temporal, left frontal, and cerebellar areas (Debas et al., 2010). Based on age-related reductions in sleep spindle oscillations (Fogel et al., 2014; Peters et al., 2008), which most likely play an important role in the consolidation of newly acquired motor skills, we expected to find age-related differences in brain activation changes after an offline period. However, we found no such differences. Perhaps this is because there were no age-related behavioral differences after the 24 h offline period, indicating that the motor skill was consolidated similarly in young and old adults. Additional research using a variety of motor tasks with additional experimental manipulations is required to further examine whether brain activation changes after an offline period involving a night of sleep are age-dependent.

4.5. There are age-related differences in brain deactivation changes

In contrast to changes in brain activation, changes in brain deactivation were age-dependent. After the motor memory consolidation phase, deactivation increased (i.e., greater deactivation) in young adults in bilateral precuneus and left occipital/angular and temporal areas and deactivation tended to increase in left inferior frontal cortex (<10 voxels). However, older adults decreased or tended to decrease brain deactivation in all of these areas (i.e., smaller deactivation). As expected, we found age-related differences in frontal and temporal areas. However, contrary to previous findings using motor sequence learning (Fogel et al., 2014), our study demonstrated effects of age on changes in deactivations instead of activations after the offline period. Our results could be explained by the fact that the precuneus, angular and temporal area are part of the DMN (Raichle et al., 2001; Raichle, 2015). Interestingly, this modulation of deactivation is age-dependent and occurs only after motor memory consolidation. Apparently, older adults do not modulate the DMN in order to consolidate and retain the skill, which is in agreement with the idea that DMN modulation is dysregulated with increasing age (Park and Reuter-Lorenz, 2009). Perhaps activating brain areas to a greater extent as shown in the Older > Young effect (see section 4.3) is a possible mechanism of compensation.

4.6. Limitations

One limitation is that, sporadically, noise occurred in the wrist position signal of the manipulandum. In the behavioral data, we used a second order low-pass Butterworth filter of 5 Hz to account for this noise. In the second model of the fMRI analyses, examining the effects of Time

and the Age × Time interaction, we subtracted the brain activation during the control condition from the brain activation during the experimental condition. We believe that the noise in the manipulandum signal had no or minimal influences on these results since any brain activation that might be related to the occurrence of the noise in the manipulandum signal occurred in both experimental and control conditions and would therefore be filtered from the data. However, the comparison of brain activation between young and older adults in the first model should be taken with some caution since the noise occurred more often in older compared with young adults and we did not contrast Experimental > Control in this model. Another limitation is that not all participants participated in the study at similar times of the day. These diurnal variations could have affected neuroplasticity (Sale et al., 2008). A final limitation was that our fMRI volumes did not completely cover the cerebellum. Since the cerebellum is known to be involved in motor learning (Daselaar et al., 2003; Fogel et al., 2014; Lefebvre et al., 2012; Rieckmann et al., 2010) and eye-hand coordination (Miall et al., 2001), our results could have underestimated the role of the cerebellum.

5. Conclusions

Age-related changes in brain activation after acquiring and consolidating a visuomotor tracking skill were examined. While there were age-related impairments in motor performance, older adults learned the skill as well as young adults. Changes in parietal and occipital activation, independent of age, suggest changes in visuospatial processing efficiency throughout the stages of motor learning. Finally, age-related deteriorations in modulating the activity of areas of the DMN after motor memory consolidation suggest that older adults use compensatory mechanisms to achieve similar learning rates as young adults. Presumably, this is achieved by activating brain areas to a greater extent during motor task execution.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.11.010.

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